CLINICAL REVIEW

Osteoporosis
Section 1: Epidemiology and aetiology

Osteoporosis causes substantial morbidity and its incidence is rising as the population ages. Management includes lifestyle advice and pharmacological interventions. By Professor John A Kanis and Dr Eugene McCloskey

ABSTRACT

Osteoporosis results in more than 200,000 fractures each year in the UK. Its diagnosis relies on quantitative assessment of bone mineral density (BMD), usually by DXA. Management can include calcium and vitamin D supplementation, plus lifestyle advice such as avoiding smoking and high alcohol intake.

Key words
Osteoporosis, fracture, bone mineral density, calcium, vitamin D

The clinical significance of osteoporosis lies in the fractures that arise. In the UK, osteoporosis results in more than 200,000 fractures each year, causing severe pain and disability to patients at an annual cost to the NHS of more than £1.73 billion.

More than one-third of adult women and one in five men will sustain one or more osteoporotic fractures in their lifetime. Hip fractures alone account for more than 20 per cent of orthopaedic bed occupancy in the UK and most of the direct health service cost of osteoporosis. Approximately 50 per cent of patients experiencing a hip fracture can no longer live independently and 20 per cent die within 12 months of the fracture.

Fractures in patients aged over 60 years account for more than two million hospital bed days in England each year. This exceeds the bed occupancy attributable to diabetes, IHD, heart failure or COPD. The ageing of the UK population will double the number of osteoporotic fractures over the next 50 years if changes are not made in present practice.

Already, the admission rate for hip fractures has increased in England by 2.1 per cent per year since 1999, while hospital bed days have increased by 5.9 per cent per year.

AETIOLOGY

The most common cause of osteoporosis arises from estrogen deficiency that begins some years before the menopause. The skeleton comprises approximately 20 per cent trabecular bone and 80 per cent cortical bone and undergoes a continual process of resorption and formation, governed by the activity of bone cells in bone remodelling units. Approximately 10 per cent of the adult skeleton is remodelled every year.

Estrogen deficiency accelerates the normal turnover of bone tissue, but the net activity of bone resorbing cells (osteoclasts) is greater than that of bone forming cells (osteoblasts). This gives rise to thinning of the cortices of bones, thinning of trabecular bone and loss of trabecular elements (figure 1). The architectural changes weaken bone disproportionately compared with the loss of skeletal mass.

The rate of loss of bone tissue is particularly rapid around the time of the menopause, giving rise to postmenopausal osteoporosis, but bone loss continues throughout later life in men as well as women. Many other disorders can give rise to osteoporosis (see box 1) by accelerating bone loss.
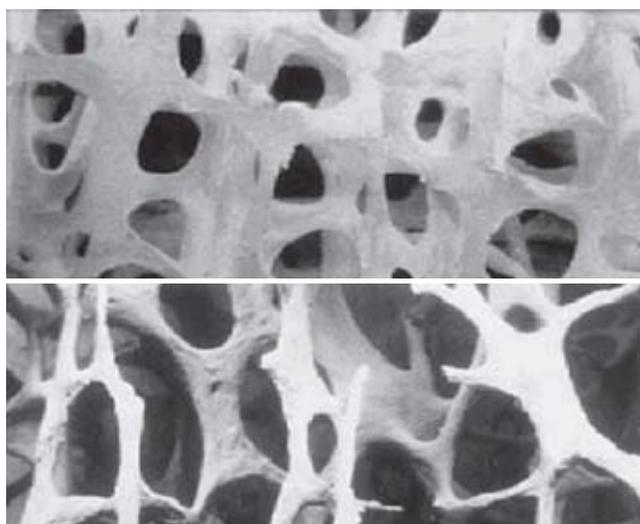

Figure 1: Comparison of structure of trabecular bone in health (upper panel) and osteoporosis (lower panel); architectural damage includes trabecular thinning and perforation

BOX 1: COMMON CAUSES OF SECONDARY OSTEOPOROSIS

Endocrine malignancy drugs
- Thyrotoxicosis
- Primary hyperparathyroidism
- Cushing's syndrome
- Hypogonadism, including anorexia nervosa
- Type-1 diabetes

Gastrointestinal
- Malabsorption syndrome, for example, coeliac disease, partial gastrectomy
- Inflammatory bowel disease
- Liver disease, for example, primary biliary cirrhosis

Rheumatological
- Rheumatoid arthritis
- Ankylosing spondylitis

Malignancy
- Multiple myeloma
- Cancer treatment induced bone loss (see below)

Drugs
- Glucocorticoids
- Anticonvulsants
- Heparin
- Aromatase inhibitors
- Androgen deprivation therapy

OSTEOPOROSIS
Section 2: Diagnosis and clinical features

The clinical features of osteoporosis are a consequence of the fractures that arise. Common sites of fracture (figure 2) include the vertebral bodies, distal radius, proximal femur and the proximal humerus. Non-vertebral fractures are easily detected by the associated acute pain and deformity, both of which will resolve with appropriate management.

In contrast, vertebral fractures are often undiagnosed because of a relative lack of symptoms (detected on X-ray only) or the attribution of back pain to other causes. Multiple vertebral fractures commonly cause symptoms and may give rise to a thoracic kyphosis and long-term morbidity.

The diagnosis of osteoporosis relies on quantitative assessment of BMD, usually by DXA. BMD at the femoral neck provides the reference site. It is defined as a value for BMD 2.5 SD or more below the young female adult mean (T-score ≤ -2.5 SD).

Severe (established) osteoporosis describes osteoporosis in the presence of one or more fragility fractures. Other indications for bone densitometry include monitoring of treatment, determining the extent of bone loss and assessment of suitability for certain treatments.

Diagnostic thresholds differ from intervention thresholds for several reasons. First, the fracture risk varies with age, even with the same T-score. Other factors that determine intervention thresholds include the presence of clinical risk factors and the cost and benefits of treatment.

INVESTIGATIONS
The aims of the clinical history, physical examination and clinical tests are to exclude diseases that mimic osteoporosis (for example, osteomalacia, myeloma), identify secondary causes of osteoporosis and contributory factors, assess the risk of subsequent fractures and select the most appropriate form of treatment. Relevant tests are shown in box 2.

Figure 2: The wrist, spine and hip (left to right) are typical sites of osteoporotic fracture

BOX 2: INVESTIGATIONS IN OSTEOPOROSIS

Routine
- History and physical examination
- FBC, ESR or CRP, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
- TFTs
- Bone densitometry (DXA)

Other investigations, if indicated
- Lateral radiographs of lumbar and thoracic spine/ DXA-based vertebral imaging
- Protein immunoelectrophoresis; urinary Bence-Jones proteins
- Serum testosterone, SHBG, FSH, LH (in men)
- Serum prolactin
- 24-hour urinary cortisol/dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
- Isotope bone scan
- Markers of bone turnover, when available
- Urinary calcium excretion

OSTEOPOROSIS
Section 3: Management options

Management of acute osteoporotic fracture is the same as that for non-osteoporotic fracture. It is important to restore mobility as soon as possible because immobilisation is an important cause of bone loss.

Lifestyle advice includes intakes of 1,000mg per day calcium, 800IU vitamin D and 1g per kg body weight protein. Smoking and high intakes of alcohol are recognised risk factors for fractures and are to be avoided. Many fractures occur after a fall and strategies to avoid falls should be considered.

ASSESSING FRACTURE RISK
The longer-term management of osteoporosis requires the assessment of future fracture risk which, in turn, determines the need for intervention.

At present there is no accepted policy for population screening in the UK to identify patients with osteoporosis or those at high risk of fracture. Rather, patients are identified opportunistically using a case-finding strategy on the finding of a previous fragility fracture or the presence of significant clinical risk factors (see box 3).

Some of these risk factors act independently of BMD to increase fracture risk, whereas others increase fracture risk

BOX 3: CLINICAL RISK FACTORS FOR OSTEOPOROSIS

- Age
- Sex
- Low BMI (19kg/m^2 or lower)
- Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
- Parental history of hip fracture
- Current glucocorticoid treatment (any dose, oral for three months or more)
- Current smoking
- Alcohol intake of three or more units daily
- Secondary causes of osteoporosis, including RA, untreated hypogonadism in men and women, prolonged immobility, organ transplantation, type-1 diabetes, hyperthyroidism, GI disease, chronic liver disease, COPD
- Falls (not accommodated in the FRAX algorithm)

through their association with low BMD. Algorithms that integrate clinical risk factors for fracture risk have been developed by WHO. The FRAX tool (www.shef.ac.uk/FRAX)

computes the 10-year probability of hip fracture or major osteoporotic fracture. The National Osteoporosis Guideline Group (NOGG) has recently published a new guideline that integrates FRAX with clinical management algorithms.

This approach adopts the previous guidance in that treatment should be considered when a patient's probability of fracture is comparable to, or exceeds that of, a woman of the same age who has already sustained a low trauma fracture.

The guideline suggests that fracture probability should be assessed with FRAX in postmenopausal women and in men aged 50 years or more with clinical risk factors where assessment would influence management.

Women with a prior fragility fracture can be considered for treatment without the need for further risk assessment, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women. In the presence of other clinical risk factors, the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) should be determined using FRAX.

Men and women with probabilities below the lower assessment threshold can be reassured. Those with probabilities above the lower assessment threshold but below the upper assessment threshold can be considered for testing with BMD using DXA and have their fracture probability reassessed. Men and women with probabilities above the upper assessment threshold should be considered for treatment.

In men and women who require a BMD test, fracture probabilities should be recomputed with FRAX. Treatment can be considered in those in whom fracture probabilities lie above the intervention threshold.

OSTEOPOROSIS
Section 4: Pharmacological interventions

Bisphosphonates, strontium ranelate, raloxifene and parathyroid hormone peptides have been shown to reduce the risk of vertebral fracture when given with calcium and vitamin D. Some of these drugs have also been shown to reduce the risk of non-vertebral fractures, in some cases specifically at the hip (see box 4).

Alendronate is the first-line treatment in most patients. In those who are intolerant of alendronate or in whom it is contraindicated, other bisphosphonates, strontium ranelate or raloxifene may provide appropriate treatment options. The high cost of parathyroid hormone peptides restricts their use to those at very high risk, particularly of vertebral fractures.

Alendronate, risedronate, zoledronate and teriparatide are also approved for treatment of men at high risk of fracture. Alendronate is approved for the prevention and treatment of glucocorticoid-induced osteoporosis.

Risedronate and etidronate are approved for the prevention and treatment of glucocorticoid-induced osteoporosis in postmenopausal women, while zoledronate is approved for the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in postmenopausal women and in men at increased risk of fracture. Teriparatide is approved for treatment of glucocorticoid-induced osteoporosis in men and women at increased risk of fracture.

Other approved treatments for postmenopausal women include calcitonin, calcitriol, etidronate and HRT.

In the near future, therapies for osteoporosis will include other selective estrogen receptor modulators and denosumab, a novel monoclonal antibody therapy that inhibits osteoclast activity via inhibition of the RANKL/RANK pathway. ∎

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